

**AMENDMENTS TO THE CLAIMS:**

This listing of claims will replace all prior versions of claims in the application:

1. (Currently Amended)      A method of identifying, screening, characterizing or designing a chemical entity that binds a FIH (Factor Inhibiting HIF (Hypoxia Inducible Factor)), comprising:

(a) comparing a structural model of a polypeptide comprising SEQ ID NO:30, or a fragment thereof that retains asparaginyl hydroxylase activity, having a 3-dimensional structure defined by the structural coordinates of structures 1, 2, or 3 in Table 3 with a structural model of a chemical entity;

(b) processing said structural coordinates of said polypeptide and said structural model of said chemical entity in a computer-based program; and

(c) identifying said chemical entities whose structure is complementary to part of said 3-dimensional structure of said polypeptide ~~which mimics or binds to a FIH (Factor Inhibiting HIF (Hypoxia Inducible Factor)) polypeptide comprising SEQ ID NO:21, or a fragment or mutant thereof that adopts a similar 3-dimensional structure as described by the structural factors or structural coordinates shown in Table 3 and wherein the fragment or mutant retains asparaginyl hydroxylase activity, which method comprises comparing a structural model of said FIH with a structural model for said chemical entity, wherein said structural model of said FIH is derived from structural factors or structural coordinates shown in Table 3.~~

2. (Cancelled).

3. (Cancelled).

4. (Currently Amended) A method according to claim 1, further comprising:  
identifying said chemical entity whose structure is complementary to one or more amino acid  
residues of said polypeptide, selected from Tyr145, Leu186, Leu188, Thr196, Phe207, Thr196,  
Lys214, and Ile281~~wherein said chemical entity binds to the FIH.~~

5. (Currently Amended) A method according to claim 4, wherein said chemical  
entity is predicted by said computer-based program to form hydrophobic interactions with any or  
all of the side chains of one or more amino acid residues of said polypeptide, selected from  
Leu186, Leu188, Thr196, Phe207, and Ile281~~1, wherein said chemical entity is selected to~~  
~~inhibit the asparaginyl hydroxylase activity of the FIH.~~5. .

6. (Currently Amended) A method according to claim 1, further comprising-  
~~contacting said chemical entity with a HIF polypeptide comprising SEQ ID NO:24 or 25 or a~~  
~~fragment thereof or a variant having at least 90% identity thereof wherein said fragment or~~  
~~variant comprises the asparagine residue therein and retains the capacity to bind to FIH, and with~~  
~~the FIH polypeptide or fragment or mutant thereof and monitoring for hydroxylation of said~~  
~~asparagine residue;~~

(a) contacting a test substance based on said structural model of said chemical entity whose  
structure was identified as being complementary to part of said 3-dimensional structure of said  
polypeptide with a polypeptide comprising SEQ ID NO:33 and a polypeptide comprising SEQ  
ID NO:30, or a fragment thereof that retains asparaginyl hydroxylase activity;

(b) monitoring for hydroxylation of said asparagine residue of said polypeptide comprising SEQ ID NO:33; and

(c) identifying said test substance that inhibits the hydroxylation of said asparagine of said polypeptide comprising SEQ ID NO:33 by said polypeptide comprising SEQ ID NO:30, or a fragment thereof that retains asparaginyl hydroxylase activity.

7. (Withdrawn) A chemical entity identified by a method according to claim 1, wherein said chemical entity inhibits the asparaginyl hydroxylase activity of FIH.

8. (Withdrawn) A chemical entity according to claim 7 wherein said chemical entity inhibits hydroxylation of the asparagine position 803 of HIF by FIH.

9. (Withdrawn) A chemical entity according to claim 7 wherein said chemical entity inhibits dimerisation of FIH.

10. (Withdrawn) A chemical entity according to claim 9 wherein said chemical entity binds to residues that form the dimerisation interface of FIH, selected from residues 330 to 346 of FIH.

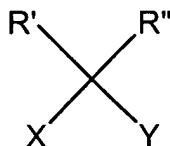
11. (Withdrawn) A chemical entity according to claim 7 wherein said chemical entity binds to iron, or prevents Fe(II) binding to FIH.

12. (Withdrawn) A chemical entity according to claim 11, wherein said chemical entity is a compound selected from a thiol, alcohol, phenol, carboxylate, hydroxamate, imidazole or other heterocyclic compound, that binds to iron.

13. (Withdrawn) A chemical entity according to claim 7 wherein said chemical entity disrupts 2-oxoglutarate binding to FIH.

14. (Withdrawn) A chemical entity according to claim 13, wherein said chemical entity is R-entiomer of N-oxaloylalanine, procollagen prolyl-hydroxylase and a PHD isozyme.

15. (Withdrawn) A chemical entity according to claim 13, wherein said chemical entity is a compound of the formula

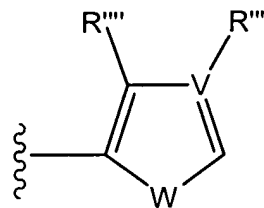
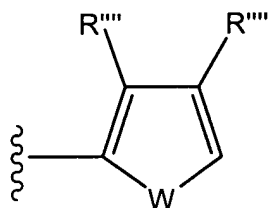
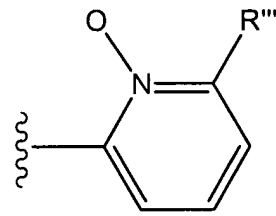
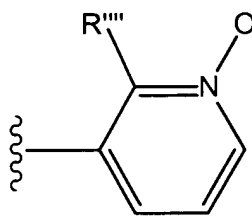
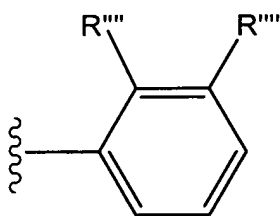


(I)

wherein each of R' and R'', which may be the same or different, is H, F or C<sub>1</sub> to C<sub>3</sub> alkyl or substituted alkyl, CH<sub>2</sub>OH, CH<sub>2</sub>CO<sub>2</sub>H or CONH<sub>2</sub>, X is COOH, SOOH, or CONHH or an ester thereof, or other group which forms a favourable interaction with one or more of the side chains of Lys-214, Thr-196 and Tyr-145,

Y is - (CR'''R''')<sub>n</sub>Z, where Z is

-NR<sup>'''</sup>COCOOH, -NR<sup>'''</sup>CSCOOH, -NR<sup>'''</sup>COCOSH, -CHSR<sup>'''</sup>CONR<sup>'''</sup>R<sup>'''</sup>,  
-CHOR<sup>'''</sup>CONR<sup>'''</sup>OR<sup>'''</sup>, -CHSR<sup>'''</sup>CONR<sup>'''</sup>OR<sup>'''</sup> or -CHOR<sup>'''</sup>CONR<sup>'''</sup>NR<sup>'''</sup>OR<sup>'''</sup>, wherein each R<sup>'''</sup>,  
which may be the same or different, is H, alkyl, OH or O-alkyl, n is 0 to 3, or



wherein R<sup>'''</sup> is OH, OR<sup>'''</sup> or NHCOR<sup>'''</sup>, and W is S, NH, or O;

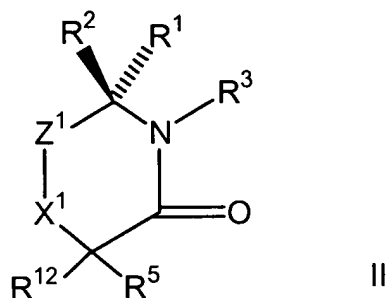
16. (Withdrawn) A chemical entity according to claim 13 wherein said chemical entity interferes with the interactions at residues 214, 196 and 145 of FIH, or which interrupts the interactions of 2OG with residues 281, 186, 188, 207 or 196 of FIH.

17. (Withdrawn) A chemical entity according to claim 16 wherein said chemical entity interrupts binding of FIH for Asn 803 of HIF, preferably, by interfering with binding of HIF at residues 102, 239 or 238 of HIF.

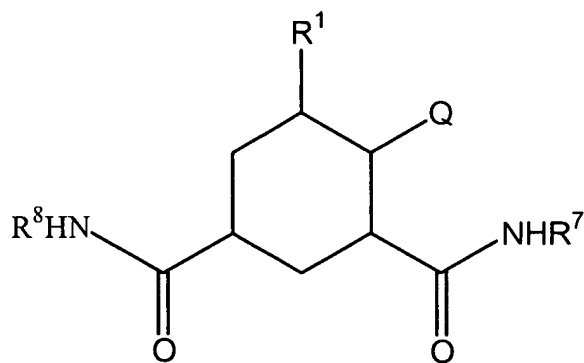
18. (Withdrawn) A chemical entity according to claim 17 which interferes with Site 1 binding of CAD of HIF to FIH and which exploits electrostatic, hydrogen binding and/or hydrophobic interactions with one or more residues selected from 102, 104, 106, 201, 202, 147, 239, 299-303, 313, 317, 318, 321, 324, 238, 296 or 321 to 324 of FIH.

19. (Withdrawn) A chemical entity according to claim 17 wherein said chemical entity interferes with binding of CAD of HIF to FIH at Site 2, and exploits electrostatic, hydrogen binding and/or hydrophobic interactions with residues 149, 150, 151, 152, 159, 162, 163, 167, 181, 182, 183, 184 or 185.

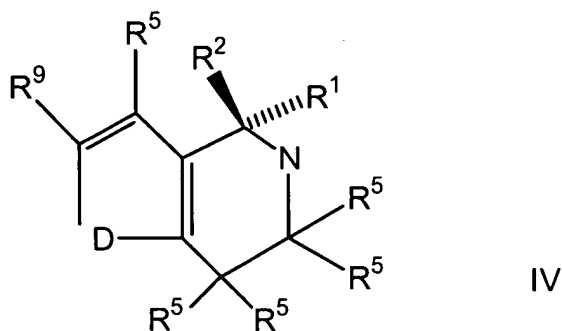
20. (Withdrawn) A chemical entity according to claim 17 wherein said chemical entity is a compound of the formula



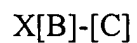
21. (Withdrawn) A chemical entity according to claim 17, wherein said chemical entity is a compound of the formula



22. (Withdrawn) A chemical entity according to claim 17 wherein said chemical entity is a compound of the formula

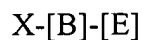


23. (Withdrawn) A chemical entity according to claim 17 wherein said chemical entity is a compound of the formula



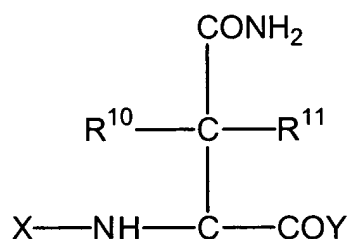
where X is as defined above, B is a linker group and C is an entity binding to part of the CAD binding site of FIH;

24. (Withdrawn) A chemical entity according to claim 17 wherein said chemical entity is a compound of the formula



where X and B are as defined above and E is an entity binding to part of the CAD when bonded to HIF.

25. (Withdrawn) A chemical entity according to claim 7 wherein said chemical entity is a compound of the formula



wherein X represents a valine residue or an analogue thereof and Y represents an alanine residue or an analogue thereof,  $\text{R}^{10}$  is fluorine or  $\text{C}_1 - \text{C}_3$  alkyl, and  $\text{R}^{11}$  is fluorine,  $\text{C}_1 - \text{C}_3$  alkyl or hydrogen or a corresponding compound  $\text{R}^{11}$  is absent or  $\text{R}^{10}$  and  $\text{R}^{11}$  form a methylene group.

26. Cancelled

27. (Withdrawn) A method of treatment of a condition associated with increased or decreased HIF levels or activity or the treatment of a condition where it is desired to modulate HIF activity, which comprises administering to a patient a chemical entity according to claim 7.



28. (Withdrawn) A method according to claim 27 wherein said condition is ischaemia, wound healing, auto-, allo- or xeno-transplantation, systemic high blood pressure, cancer or an inflammatory disorder.

29. (Currently Amended) A method of identifying, screening, characterizing or designing a chemical entity which inhibits the asparaginyl hydroxylation of a HIF polypeptide by a FIH polypeptide, comprising:

(a) comparing a structural model of a polypeptide comprising SEQ ID NO:30 co-crystallized with a polypeptide comprising SEQ ID NO:33, having a 3-dimensional structure defined by the structural coordinates of structures 1, 2, or 3 in Table 3 with a structural model of a chemical entity;

(b) processing said structural coordinates of said polypeptides and said structural model of said chemical entity in a computer-based program; and

(c) identifying said chemical entities whose structure is predicted to inhibit the interaction between said polypeptide comprising SEQ ID NO:30 and a  $\beta$ -carbon of an asparagine residue of said polypeptide comprising SEQ ID NO:33-mimies or binds to a FIH (Factor Inhibiting HIF- (Hypoxia Inducible Factor)), polypeptide comprising SEQ ID NO:21, or a fragment or mutant thereof, that adopts a similar 3-dimensional structure as described by the structural factors or structural coordinates shown in Table 3, and wherein the fragment or mutant retains asparaginyl-hydroxylase activity, which method comprises using the structural coordinates shown in Table 3 and identifying, screening, characterizing or designing said chemical entity that mimics or binds to said FIH.

30. (Cancelled)

31. (Currently Amended) A method according to claim 29, further comprising:  
identifying said chemical entity that is complementary to one or more amino acid residues of  
said polypeptide comprising SEQ ID NO:30, selected from Tyr145, Leu186, Leu188, Thr196,  
Phe207, Thr196, Lys214, and Ile281~~wherein said chemical entity binds to the FII.~~

32. (Currently Amended) A method according to claim ~~[[29]]~~31, wherein said  
chemical entity is identified by said computer-based program to form hydrophobic interactions  
with any or all of the side chains of one or more amino acid residues of said polypeptide selected  
from Leu186, Leu188, Thr196, Phe207, and Ile281~~selected to inhibit the asparaginyl-~~  
~~hydroxylase activity of the FII.~~

33. (Currently Amended) A method according to claim 29, further comprising:  
(a) contacting a test substance based on said structural model of said chemical entity whose  
structure was predicted to inhibit said interaction between a  $\beta$ -carbon of an asparagine residue of  
said polypeptide comprising SEQ ID NO:33 and said polypeptide comprising SEQ ID NO:30  
with a polypeptide comprising SEQ ID NO:33 and a polypeptide comprising SEQ ID NO:30;  
(b) monitoring for hydroxylation of said asparagine residue of said polypeptide comprising SEQ  
ID NO:33; and  
(c) identifying said test substance that inhibits the hydroxylation of said asparagine of said  
polypeptide comprising SEQ ID NO:33 by said polypeptide comprising SEQ ID NO:30-  
~~contacting said chemical entity with a HIF polypeptide comprising SEQ ID NO:24 or 25 or a~~

~~fragment thereof or variant having at least 90% identity thereof, wherein said fragment or variant retains the asparagine residue therein and retains the capacity to bind FIH, and with the FIH polypeptide or fragment or mutant thereof, and monitoring for hydroxylation of said asparagine residue.~~

34. (New) A method according to claim 4, wherein said chemical entity is identified by said computer-based program to form electrostatic or hydrogen bonding interactions with one or more amino acid residues of said polypeptide, selected from Tyr145, Thr196, and Lys214.

35. (New) A method according to claim 31, wherein said chemical entity is identified by said computer-based program to form electrostatic or hydrogen bonding interactions with one or more amino acid residues of said polypeptide, selected from Tyr145, Thr196, and Lys214.